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Effect of dietary modification on urinary stone risk factors

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Background. This study was undertaken to ascertain the effect of dietary modification on urinary stone risks, and to determine whether the response depends on the prevailing urinary calcium.

Methods. A retrospective data analysis was conducted from our stone registry involving 951 patients with calcareous stones undergoing ambulatory evaluation, whereby 24-hour urine samples were collected during random diet and after dietary modification composed of restriction of calcium, oxalate, sodium, and meat products. Samples were analyzed for stone risk factors. Urinary calcium was also obtained after overnight fast and following a 1 g-calcium load. Changes produced by dietary modification from the random diet were evaluated in 356 patients with moderate-severe hypercalciuria (>6.88 mmol/day, group I), 243 patients with mild hypercalciuria (5.00–6.88 mmol/day, group II), and 352 with normocalciuria (<5.00 mmol/day, group III).

Results. Urinary calcium postcalcium load and the percentage of patients with absorptive hypercalciuria type I were highest in group I, intermediate in group II, and lowest in group III. During dietary modification, urinary calcium declined by 29% in group I, 19% in group II, and 10% in group III. Urinary oxalate did not change. Urinary saturation of calcium oxalate declined by only 12% in group I, 6% in group II, and nonsignificantly in group III, owing to various physicochemical changes in urinary biochemistry, which attenuated the effect of the decline in urinary calcium. Urinary saturation of brushite declined in all 3 groups due to the fall in urinary calcium, phosphorus, and pH. This reduction was more marked in the hypercalciuric groups than in the normocalciuric group. Urinary saturation of monosodium urate also decreased from a decline in urinary sodium and uric acid.

Conclusion. Secondary rise in urinary oxalate occurring from calcium restriction can be avoided by concurrent dietary oxalate restriction. Dietary modification (restriction of dietary calcium, oxalate, sodium, and meat products) is more useful in reducing urinary saturation of calcium oxalate among patients with hypercalciuria than among those with normocalciuria.

There is some uncertainty regarding the value of dietary calcium restriction in the management of calcium nephrolithiasis. Epidemiologic studies in the 1990s showing the protective effect of dietary calcium on stone formation have led to the reexamination of the widely held practice of dietary calcium restriction [1, 2]. A recent randomized trial disclosed that a diet restricted in sodium and animal proteins but liberal in calcium and fruit products is more effective than a diet restricted in calcium in preventing stone formation [3].

However, a metabolic study [4] showed that the protective effect of high dietary calcium may have resulted from concurrent increased intake of protective dietary factors—fluids, potassium, and magnesium. The aforementioned diet trial [3] lacked an appropriate control group for the low calcium diet, since the two diets differed in more than their calcium content. Moreover, a detailed examination of data from our stone registry indicated that urinary calcium was equally important as urinary oxalate in determining urinary saturation of calcium oxalate among patients with predominantly calcium oxalate stones [5]. Among those with calcium phosphate stones, urinary calcium was a key determinant of urinary saturation of brushite ($CaHPO_4 \bullet H_2O$), but urinary oxalate was not [6]. In normal subjects, calcium carbonate supplementation increased urinary saturation of calcium oxalate [7], but this rise was attenuated by calcium citrate supplementation [8, 9]. Among patients with stones suffering from absorptive hypercalciuria type I (AH-I) with enhanced intestinal calcium absorption, a high calcium intake produced a much more marked increase in urinary calcium than in normal subjects [10].

The apparently conflicting reports described above have led to a general confusion regarding the recommendation for calcium intake during the management of stone disease. Multiple factors can potentially influence the way calcium intake modifies urinary saturation of calcium oxalate. A change in calcium content of the diet is often

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accompanied by alteration in other components [1, 2, 4]. The dietary recommendation for the control of stone formation often imposes changes in other food components besides calcium-rich foods [3], such as oxalate, sodium [11], and purines. Moreover, the response to alteration in calcium intake depends on the prevailing intestinal calcium absorption of the patients [10].

In order to identify the effects the various factors that modify the action of dietary calcium described above, and to seek a rational basis for dietary management in calcium nephrolithiasis, we conducted a retrospective data analysis of urinary stone risks from 951 patients with stones who underwent a detailed ambulatory evaluation [13]. This evaluation involved collection of 24-hour samples before and after a dietary modification that comprised a restriction of calcium, oxalate, sodium, and meat. Patients were divided into 3 groups according to 3 ranges of urinary calcium excretion during the random diet. By comparing the effect of this dietary modification on urinary stone risk factors between the 3 groups, it was possible to examine interaction between various dietary changes and to test the hypothesis that the beneficial effect of dietary modification depended on the presence or absence of, and the degree of, hypercalciuria.

METHODS

Patient data

From our stone registry of 2200 patients with stones who underwent our ambulatory evaluation [13], data were retrieved from patients who satisfied the following entry criteria: (*1*) ≥18 years of age of either gender or ethnicity; (*2*) availability of stone analysis; (*3*) stone composition showing calcium oxalate and/or calcium phosphate (hydroxyapatite or brushite); (*4*) 1 or 2 24-hour urine collections on a "random diet," and a 24-hour urine collection on a "restricted diet" for the analysis of stone risk factors [14]; and (*5*) adequacy of urine collection, indicated by urinary creatinine ± 30% of idealized urinary creatinine (22.1 mg/kg in men and 17.2 mg/kg creatinine in women) [15]. Exclusion criteria were: (*1*) stone composition showing struvite, carbonate apatite, or tricalcium phosphate; (*2*) infection of the urinary tract with urea-splitting organisms; (*3*) primary hyperparathyroidism or hypercalcemia; and (*4*) moderate-severe chronic diarrheal syndrome due to organic diseases of the bowel (ileal resection, bypass surgery, Crohn's disease, fat malabsorption).

Nine hundred and fifty-one patients satisfied the above criteria. They were divided into 3 groups, based on 24-hour urinary calcium during the random diet. Group I (moderate-severe hypercalciuria) comprised patients whose urinary calcium exceeded 6.88 mmol (275 mg)/day. Patients in group II (mild hypercalciuria) had urinary calcium ranging from 5.00 to 6.88 mmol/day (200–275 mg/day). Group III (normocalciuria) were those with urinary calcium <5.00 mmol (200 mg)/day. In each group, the following data were extracted: gender, age, height, weight, percentage of patients with predominantly calcium oxalate stones (>70% calcium oxalate) and percentage with calcium phosphate stones (≥30% calcium phosphate), family history of stones (not distinguished according to stone type), and history of stone recurrence.

Ambulatory protocol

Employed in Dallas since 1978, this protocol entailed evaluation of patients during their usual diet (random diet) and following 1 week of adherence to a restricted diet limited in calcium (10 mmol or 400 mg/day), oxalate, sodium (100 mmol/day), and meat products [13]. Patients were instructed on the restricted diet by a dietician or a trained nurse by using a published diet instruction sheet [15]. Calcium restriction was achieved by avoidance of milk and dairy products, oxalate restriction by avoidance of tea, chocolate, dark roughages, and nuts; and sodium restriction by avoiding use of salt shakers and salty prepared foods. Meat intake was limited to 2 (3 oz) servings per day or approximately 168 g of protein per day. Patients were asked to stop calcium supplements or any drug that could affect the metabolism of calcium, uric acid, or oxalate, for at least 1 week before and during each urine collection. Prior to referral to our center for evaluation, the patients were commonly advised by other physician(s) to restrict calcium intake and increase fluid ingestion, and less commonly, to reduce the intake of salt, meat products, and oxalate-rich foods.

During both diets, urine samples were collected in 24-hour pools for stone risk factors [14], which included calcium, oxalate, citrate, phosphorus, uric acid, pH, sodium, potassium, magnesium, and total volume. Some tests (sulfate, chloride, and ammonium) were not measured in all patients, since they were introduced to the assay profile at various times since the introduction of the study protocol in 1978. Some patients collected 2 random urine samples; the mean value for various stone risk factors was employed in the data to be presented.

Following the 24-hour urine collection on the restricted diet, patients underwent the study of "fast and calcium load" [16], whereby they collected a 2-hour urine sample after an overnight fast and a 4-hour urine sample following an oral load of 1 g calcium. Urine samples were analyzed for calcium and creatinine. A fasting serum sample was also obtained and analyzed for creatinine. Fasting and post-calcium load urinary calcium was expressed as μmol/dL glomerular filtrate (GF) by multiplying urinary calcium in μmol/mmol creatinine by serum creatinine in mmol/dL.

From the above tests, the diagnosis of various stone-forming conditions was made using the previously

published criteria [17]. AH-I was defined as urinary calcium >5.00 mmol/day on both random and restricted diets, and a postload urinary calcium >5 μmol/dL GF. High fasting urinary calcium (>2.75 μmol/dL GF) was allowed in order to include patients with severe AH with fasting hypercalciuria. Hyperuricosuric calcium oxalate urolithiasis (HUCU) represented urinary uric acid >3.57 mmol (600 mg)/day on all urine samples or for the mean, with urinary pH >5.5. In hypocitraturia, mean urinary citrate was <1.67 mmol (320 mg)/day.

Estimation of the intake of calcium, oxalate, sodium, and meat during the random diet

At evaluation, diet history was taken regarding the intake of key ingredients during the usual diet [15]. From all patients, this history was reviewed by a metabolic dietitian (L.J.B.) or a trained research nurse (R.D.P.), in order to categorize each intake into "mild," "moderate," and "high." Accordingly, for dietary calcium, avoidance of milk and dairy products as in the instructed diet constituted a low intake, some ingestion a moderate intake, and liberal ingestion represented a high intake. For dietary oxalate, avoidance of oxalate-rich foods as in the instructed diet indicated a low intake, consumption of some represented a moderate intake, and liberal consumption constituted a high intake. For dietary sodium, a low intake as in the instructed diet represented avoidance of salt shakers and salty foods, a moderate intake allowed some, and a high intake indicated liberal use. For meat intake, 2 servings per day represented a moderate intake as in the instructed diet, <2 servings a low intake, and >2 servings indicated a high intake. This categorization was independently evaluated by both investigators in selected patients to assure close corroboration.

Calculation of activity products

From urinary stone risk factors, relative saturation ratio (RSR) of calcium oxalate, brushite, and monosodium urate, and undissociated uric acid [18] were calculated by using the Equil 2 computer program (Department of Urology, University of Florida) [19]. RSR, the ratio of activity product and thermodynamic solubility product, was used to depict urinary saturation because it was conveniently expressed as whole numbers.

The calculation of activity product from urinary stone risk factors is briefly described here, illustrated for calcium oxalate. It should be noted that the urinary saturation of calcium oxalate is defined by the activity product ($\alpha_{Ca^{2+}} \times \alpha_{Ox^{2-}}$), not by the product of total or ionic calcium and oxalate concentrations.

$$\alpha_{Ca^{2+}} \times \alpha_{Ox^{2-}} = [Ca^{2+}]\gamma \times [Ox^{2-}]\gamma$$

where $\alpha_{Ca^{2+}}$ is the activity of calcium ion, $\alpha_{Ox^{2-}}$ is activity of oxalate ion, $[Ca^{2+}]$ the concentration of calcium ion, $[Ox^{2-}]$ concentration of oxalate ion, and γ is the activity coefficient. $[Ca^{2+}]$ is the total calcium concentration minus the concentration of soluble complexes principally of calcium-oxalate and calcium-citrate. $[Ox^{2-}]$ is the total oxalate concentration minus the concentration of soluble calcium-oxalate complexes. γ is an inverse function of ionic strength that is determined by the amount of cations and anions. $\alpha_{Ca^{2+}}$ is defined by the product of $[Ca^{2+}]$ and γ. $\alpha_{Ox^{2-}}$ is obtained as the product of $[Ox^{2-}]$ and γ.

In the Equil 2 program [19], the computer computes the amount of soluble complexes by using stability constants, and derives $[Ca^{2+}]$ and $[Ox^{2-}]$ by subtracting respective complexes from experimentally derived total calcium and oxalate concentrations. It also calculates γ from urinary analytes derived from stone risk analysis by using Debye-Huckel limiting law. When determining the activity products of brushite and monosodium urate, the concentrations of divalent phosphate (HPO_4^{2-}) and monovalent urate are obtained from the respective dissociation constants and pH. The computer program repeats these procedures (iterations), until a tight fit of data is obtained.

Statistical analysis

One way analysis of variance (ANOVA) was used to assess significant differences in laboratory data obtained during the random diet between the 3 groups. When ANOVA reached significance, individual comparison between groups was made by least squares means probabilities with Bonferoni corrections. For each group, paired *t* tests were used to assess significant differences between the random diet and restricted diet. For ordered categorical analysis (estimate of dietary intakes), overall group comparisons and pairwise comparisons were made with the Mantel-Haenszel correlation statistic. For stone type, family history of stones, stone recurrence, and percentage of various diagnoses, group differences were assessed with the chi-square test. Statistical analysis was performed with SAS 9.1 (SAS Institute, Cary, NC, USA). Results are expressed as mean ± standard deviation.

RESULTS

Comparison of the 3 groups

There were 356 patients in group I, 243 in group II, and 352 in group III (Table 1). While there were more men than women in all 3 groups, the male predominance was most marked in group I and least marked in group III. While age did not differ, the body height, weight, and body mass index (BMI) were higher in group I than group II, and in group II than group III. In all 3 groups, the vast majority of patients had predominantly calcium oxalate stones (~90%) rather than calcium phosphate stones. About one half of patients gave a positive family

Table 1. Demography and baseline presentation

	Group I	Group II	Group III	ANOVA *P*
No. patients	356	243	352	
Gender *M/F*	288/68	170/73	208/144	
Age	43.0 ± 10.8	41.8 ± 12.6	42.1 ± 12.3	0.4
Height *cm*	175 ± 9	173 ± 9[a]	170 ± 9[a,b]	<0.0001
Weight *kg*	86.7 ± 17.5	78.6 ± 15[a]	72.8 ± 15.9[a,b]	<0.0001
BMI kg/m^2	28.2 ± 5.4	26.2 ± 4.4[a]	25.1 ± 4.9[a,b]	<0.0001
CaOx stones% *pts*	92.1	89.5	89.9	0.9
CaP stones% *pts*	7.9	10.5	10.1	0.4
Family history of stones% *pts*	54.2	57.6	52.0	0.4
Stone recurrence% *pts*	90.4	91.5	86.9	0.15
Ca intake% *pts* Low/Moderate/High	11.8/36.1/52.1	14.2/60.8/25.0[a]	31.8/57.3/11.0[a,b]	<0.0001
Ox intake% *pts* Low/Moderate/High	14.0/52.8/33.2	18.7/57.1/25.2	18.9/58.9/22.2[a]	0.002
Na intake% *pts* Low/Moderate/High	18.1/40.4/41.5	27.0/46.5/26.6[a]	32.8/45.2/22.0[a]	<0.0001
Meat intake% *pts* Low/Moderate/High	4.7/42.9/52.5	7.9/55.8/36.3[a]	14.5/57.2/28.3[a]	<0.0001
Fasting Ca *μmol/dL GF*	2.5 ± 1.7	2.2 ± 1.2[a]	1.7 ± 1.0[a,b]	<0.0001
Load Ca *μmol/dL GF*	7.0 ± 3.0	6.0 ± 2.2[a]	5.0 ± 2.2[a,b]	<0.0001
Diagnosis, no. *(%)*				
AH-I	262 (73.6)	153 (63.0)[a]	0 (0)[a,b]	<0.0001
HUCU	213 (59.8)	94 (38.7)[a]	88 (25.0)[a,b]	<0.0001
Hypocitraturia	99 (27.8)	96 (39.5)[a]	173 (49.1)[a]	<0.0001
Urinary Ca *mmol/day*	9.18 ± 2.00	5.89 ± 0.52[a]	3.62 ± 1.05[a,b]	<0.0001
Cr clearance *mL/min*	3.07 ± 0.80	2.72 ± 0.60[a]	2.45 ± 0.95[a,b]	<0.0001

Abbreviations: Ox, oxalate; Pts, patients; P, phosphate. Group I, urinary calcium >6.88 mmol/day. Group II, urinary calcium 5.00 to 6.88 mmol/day. Group III, urinary calcium <5.00 mmol/day. Values are presented as mean ± SD. Dietary intakes indicate estimates for the random diet.
[a] $P < 0.017$ vs. group I; [b] $P < 0.017$ vs. group II.

history of stones, and most patients were recurrent stone-formers.

There were statistically significant group differences in the estimated intake of calcium, oxalate, sodium, and meat during the random diet (Table 1). The percentage of patients on high intake of calcium, oxalate, sodium, or meat was largest in group I, intermediate in group II, and smallest in group III. Conversely, the percentage of patients on low intake of these constituents was largest in group III, intermediate in group II, and smallest in group I. The majority of patients in each group took more calcium, oxalate, and sodium during the random diet than during the instructed diet for restricted urine collection. More calcium was taken during the random diet than restricted diet in 88% of patients in group I, 86% in group II, and 68% in group III. More oxalate was taken during random than restricted diet in 86% in group I, 82% in group II, and 81% in group III. More sodium was ingested during random than restricted diet in 82% in group I, 73% in group II, and 67% in group III. For meat consumption, the majority of patients in groups II and III were already on either low or moderate meat intake (63.7% and 71.7% for group II and group III, respectively). In group I, 47.6% were on low or moderate meat intake during the random diet.

Urinary calcium during fast and post-calcium load was highest in group I and lowest in group III (Table 1). AH-I was disclosed in a majority of patients in group I and group II, but was absent in group III. HUCU was encountered in a majority of patients in group I; a smaller number of patients suffered from this condition in group III than in group II. Conversely, the prevalence of hypocitraturia was lowest in group I (28%) and highest in group III (49%).

Urinary calcium on a random diet was highest in group I, intermediate in group II, and lowest in group III (Table 1). A similar pattern was noted in urinary oxalate, citrate, magnesium, phosphorus, sodium, uric acid, and endogenous creatinine clearance ($P < 0.002$ by ANOVA) (Tables 2–4).

Table 2. Comparison of random and restricted diets in group I with urinary calcium >6.88 mmol/day

	Random diet	Restricted diet	*P* value
TV *mL*	2081 ± 918	1963 ± 954	0.002
pH	5.99 ± 0.39	5.94 ± 0.41	0.01
Ca *mmol/day*	9.18 ± 2.00	6.54 ± 2.35	<0.0001
Ox *mmol/day*	0.408 ± 0.141	0.392 ± 0.160	0.0635
Cit *mmol/day*	3.01 ± 1.39	2.70 ± 1.36	<0.0001
Mg *mmol/day*	4.95 ± 1.62	4.14 ± 1.49	<0.0001
P *mmol/day*	35.7 ± 9.9	31.5 ± 10.4	<0.0001
Na *mmol/day*	208 ± 76	125 ± 64	<0.0001
K *mmol/day*	57.3 ± 19.6	53.6 ± 21.8	0.0003
UA *mmol/day*	4.05 ± 1.20	3.98 ± 1.49	0.4
SO_4 *mmol/day*	24.4 ± 9.2	23.4 ± 9.5	0.1
NH_4 *mEq/day*	42.8 ± 17.4	43.3 ± 15.3	0.8
Cr *mmol/day*	15.9 ± 3.6	15.8 ± 3.8	0.3
RSR CaOx	9.94 ± 4.22	8.76 ± 3.94	<0.0001
RSR Br	3.21 ± 1.79	2.22 ± 1.65	<0.0001
RSR NaU	3.81 ± 2.46	2.69 ± 2.35	<0.0001
H_2U *mmol/day*	0.839 ± 0.571	0.899 ± 0.625	0.1

Abbreviations are: Ox, oxalate; Cit, citrate; UA, uric acid; Cr, creatinine; RSR, relative saturation ratio; CaOx, calcium oxalate; Br, brushite; NaU, monosodium urate; H_2U, undissociated uric acid.

Table 3. Comparison of random and restricted diets in group II with urinary calcium 5.00 to 6.88 mmol/day

	Random diet	Restricted diet	*P* value
TV *mL*	1795 ± 852	1727 ± 851	0.1
pH	6.03 ± 0.39	5.97 ± 0.44	0.02
Ca *mmol/day*	5.89 ± 0.52	4.74 ± 1.62	<0.0001
Ox *mmol/day*	0.364 ± 0.133	0.344 ± 0.127	0.1
Cit *mmol/day*	2.62 ± 1.34	2.27 ± 1.26	<0.0001
Mg *mmol/day*	4.05 ± 1.30	3.50 ± 1.37	<0.0001
P *mmol/day*	29.1 ± 7.5	27.1 ± 8.8	0.0003
Na *mmol/day*	170 ± 63	108 ± 50	<0.0001
K *mmol/day*	51.1 ± 18.2	45.3 ± 18.5	<0.0001
UA *mmol/day*	3.48 ± 1.01	3.32 ± 1.20	0.02
SO_4 *mmol/day*	19.6 ± 7	20.3 ± 10.1	0.2
NH_4 *mEq/day*	33.9 ± 11.8	40.8 ± 15.8	0.0001
Cr *mmol/day*	14.1 ± 3.4	14.1 ± 3.5	0.6
RSR CaOx	8.62 ± 4.01	8.09 ± 3.62	0.04
RSR Br	2.64 ± 1.72	2.07 ± 1.89	<0.0001
RSR NaU	4.07 ± 2.97	2.92 ± 2.66	<0.0001
H_2U *mmol/day*	0.673 ± 0.476	0.708 ± 0.446	0.2

Abbreviations are the same as in Table 2.

Table 4. Comparison of random and restricted diets in group III with urinary calcium <5.00 mmol/day

	Random diet	Restricted diet	*P* value
TV *mL*	1581 ± 694	1618 ± 773	0.3
pH	6.01 ± 0.44	5.96 ± 0.43	0.04
Ca *mmol/day*	3.62 ± 1.05	3.24 ± 1.37	<0.0001
Ox *mmol/day*	0.363 ± 0.215	0.355 ± 0.224	0.8
Cit *mmol/day*	2.15 ± 1.27	2.05 ± 1.21	0.3
Mg *mmol/day*	3.40 ± 1.53	3.18 ± 1.25	0.002
P *mmol/day*	25.7 ± 7.7	23.7 ± 7.9	<0.0001
Na *mmol/day*	147 ± 59	102 ± 51	<0.0001
K *mmol/day*	46.1 ± 17.4	43.3 ± 17.3	0.002
UA *mmol/day*	3.10 ± 1.01	3.08 ± 1.18	0.9
SO_4 *mmol/day*	16.6 ± 7.3	17.3 ± 7.9	0.1
NH_4 *mEq/day*	32.4 ± 16.1	34.4 ± 13.2	0.1
Cr *mmol/day*	12.6 ± 3.5	13.0 ± 3.8	0.3
RSR CaOx	6.88 ± 4.33	6.57 ± 3.58	0.09
RSR Br	1.73 ± 1.52	1.43 ± 1.35	<0.0001
RSR NaU	3.71 ± 3.12	2.74 ± 2.63	<0.0001
H_2U *mmol/day*	0.696 ± 0.530	0.702 ± 0.524	0.6

Abbreviations are the same as in legend to Table 2.

Serum calcium, phosphorous, total CO_2 content, and parathyroid hormone (PTH) concentrations were not significantly different between groups (data not shown).

Effect of dietary modification on urinary calcium and oxalate

Urinary calcium was significantly lower on the restricted diet than on the random diet in all 3 groups (Fig. 1, Tables 2–4). The decline in urinary calcium of 29% was greatest in group I with moderate-severe hypercalciuria, intermediate at 19% in group II with mild hypercalciuria, and least pronounced at 10% in group III with normocalciuria. In contrast, urinary oxalate was not significantly different between random and restricted diets in any of 3 groups.

Effect of calcium oxalate on urinary saturation

Urinary citrate was significantly lower on the restricted diet than on the random diet in groups I and II (Fig. 1, Tables 2–4). Urinary sodium was significantly lower on the restricted diet in all 3 groups.

Figure 2 displays critical physicochemical factors that determine urinary saturation of calcium oxalate, calculated and derived from the Equil 2 program [20]. The amount of soluble calcium-oxalate complex was significantly lower during restricted diet than on the random diet in groups I and II (Fig. 2), owing to a decline in urinary calcium without a change in urinary oxalate (Fig. 1). The amount of calcium-citrate complexes also decreased with the imposition of restricted diet, since both calcium and citrate declined. Activity coefficient was higher during the restricted diet than on the random diet, due largely to the lower urinary sodium. Associated with these changes, activity of calcium ion ($\alpha_{Ca^{2+}}$) decreased and activity of oxalate ion ($\alpha_{Ox^{2-}}$) increased during dietary restriction. Urinary RSR of calcium oxalate was significantly lower on the restricted diet than on random diet in groups I and II; however, the decline in RSR (of 12% and 6%) was less marked than the fall in urinary calcium (of 29% and 19%) (Fig. 2 vs. Fig. 1). There was no significant difference in the RSR of calcium oxalate between the two diets in group III, despite a 10% decrease in urinary calcium.

Effect of brushite and urate on urinary saturation

There was a small but significant decline in urinary phosphorus and pH with dietary restriction (Fig. 3, Tables 2–4). RSR of brushite declined significantly in all 3 groups. The decline was 31% in group I, 22% in group II, and 17% in group III.

Urinary uric acid did not change or decreased slightly with dietary restriction (Fig. 3). Urinary RSR of monosodium urate declined significantly in all 3 groups, but the amount of undissociated uric acid did not change.

DISCUSSION

This retrospective data analysis from our stone registry was undertaken in order to examine the effect of dietary modification (restricted in calcium, oxalate, sodium, and meat products) on urinary stone risk factors, and to identify patient population who might be most amenable to dietary management. Overall, dietary modification reduced urinary calcium, moreso among patients with moderate-severe hypercalciuria than among those with mild hypercalciuria and normocalciuria, but it did not change urinary oxalate owing to concurrent oxalate restriction. Urinary citrate decreased (probably from reduced alkali load) and urinary sodium substantially decreased (from salt restriction). Above changes in

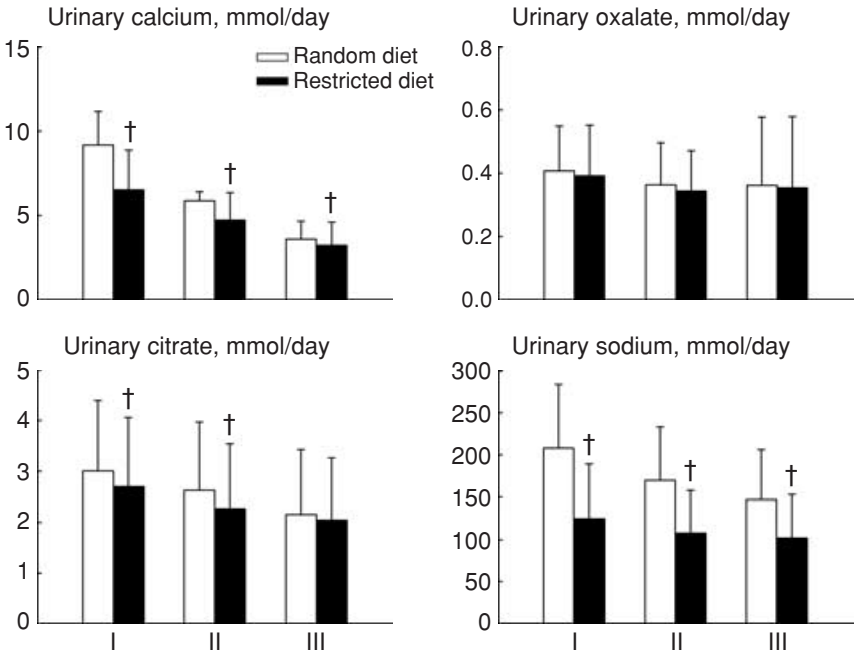

Fig. 1. Effect of dietary modification on urinary calcium, oxalate, citrate, and sodium in the 3 groups. Group I = urinary calcium during random diet >6.88 mmol/day; group II = urinary calcium 5.00 to 6.88 mmol/day; group III = urinary calcium <5.00 mmol/day. Horizontal lines above the bars indicate mean ± SD. Dagger symbol indicates $P < 0.001$ between random and restricted diets.

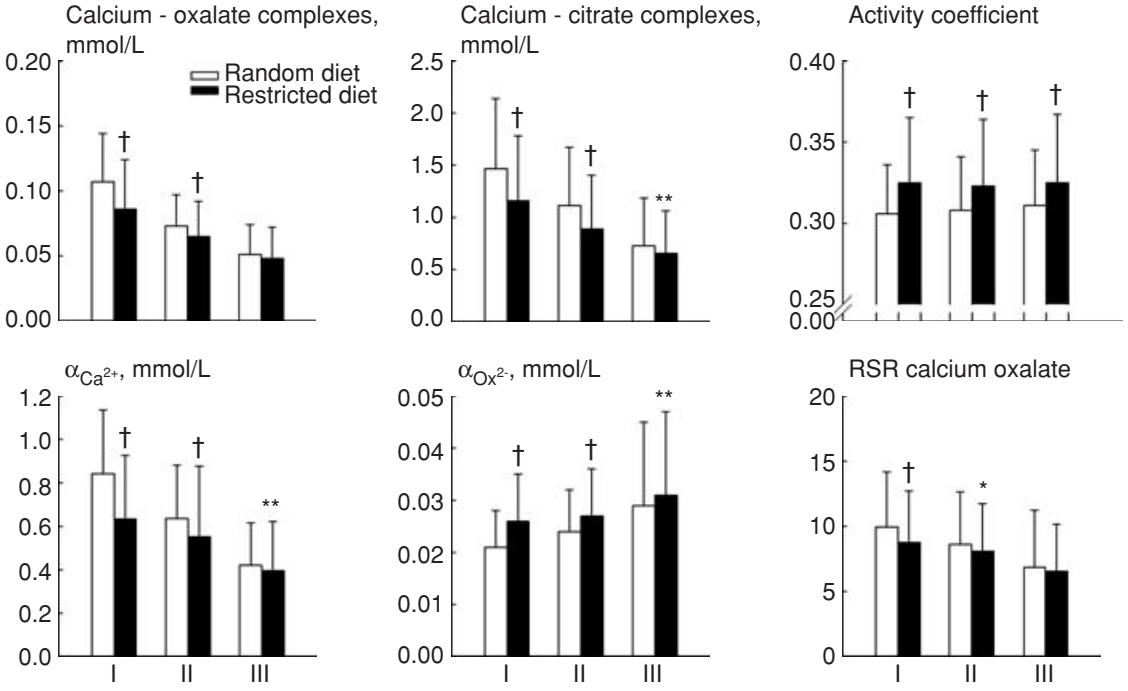

Fig. 2. Effect of dietary modification on calcium-oxalate complex, calcium-citrate complexes, activity coefficient, activity of calcium ion (Ca^{2+}), activity of oxalate ($\alpha_{Ox^{2-}}$), and relative saturation ratio (RSR) of calcium oxalate. $^{**}P < 0.01$ between the 2 diets.

urinary constituents modified the amount of soluble complexes of calcium oxalate and calcium citrate as well as the activity coefficient of urine, thereby altering the activity of calcium and oxalate ions that determine the saturation of calcium oxalate. Thus, the decline in RSR of calcium oxalate was less marked than that of urinary calcium, with a mild-modest decline among patients with hypercalciuria but no significant change in those with normocalciuria. Dietary modification also reduced urinary phosphorus and pH, reducing urinary saturation of brushite.

The original intent of the dietary modification was to simulate in an outpatient setting with an instructed diet, a constant metabolic dietary regimen accomplished in the inpatient setting of the General Clinical Research Center. The similarity of 24-hour, fasting, and postload urinary calcium between the 2 diets [20] justified the use

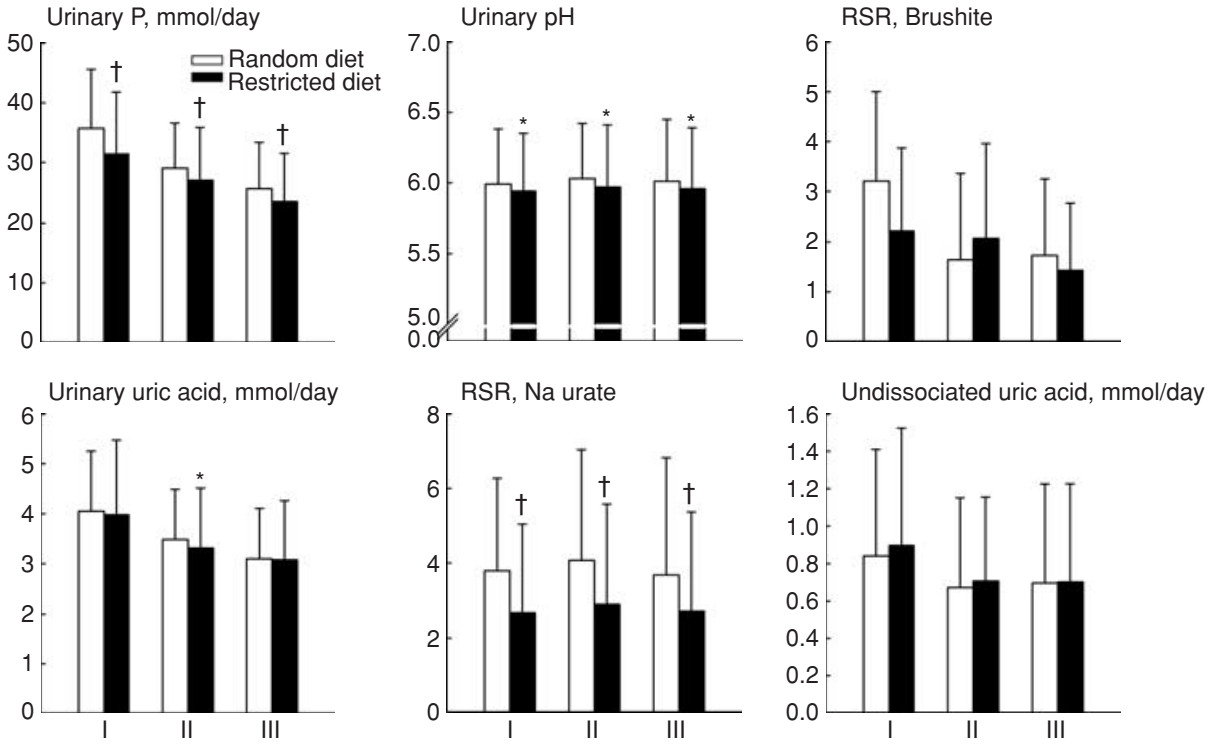

Fig. 3. Effect of dietary modification on urinary phosphorus (P), pH, RSR brushite, uric acid, RSR of monosodium urate (Na Urate), and undissociated uric acid. $^*P < 0.05$ between the 2 diets.

of an instructed diet for the evaluation of patients with urolithiasis in an ambulatory setting, particularly for the differentiation of hypercalciurias.

The dietary modification used here imposed not only a restricted intake of calcium, but also of oxalate, sodium, and meat products. This diet is not overly difficult to follow because it entailed mainly the avoidance of dairy products, oxalate-rich foods, and use of salt shakers. For this reason, it had been recommended as the basic dietary program that might be modified for specific needs during long-term management of recurrent urolithiasis [21]. There is general agreement that dietary restriction of oxalate, sodium, and meat products is beneficial in the control of stone disease [3]. While the dietary modification did not include increased intake of fruit products, it was felt that potassium citrate may serve the needs of potassium-rich citrus fruits, without the disadvantages of increased calories and mild oxaluric action of fruit products [22]. Regarding calcium intake, we had recommended earlier empirically that a calcium restriction might be imposed among patients with hypercalciuria in the absence of bone loss [21].

This study was directed toward redressing current uncertainty regarding calcium intake in the management of calcium nephrolithiasis. Broad dietary modification with changes in dietary composition other than calcium can modify urinary calcium as well as other urinary constituents that could alter urinary saturation of stone-forming salts [11, 12, 22, 23]. Moreover, a substantial fraction of patients with urolithiasis suffer from hypercalciuria due to enhanced intestinal absorption of calcium [10, 17]. Such patients may well respond differently to calcium restriction than those with normal intestinal calcium absorption.

The above predictions were met. Dietary modification restriction significantly decreased urinary calcium. The fall in urinary calcium was 29% in group I with moderate-severe hypercalciuria, 19% in group II with mild hypercalciuria and 10%, in group III with normocalciuria.

Urinary oxalate did not change significantly due to concurrent dietary oxalate restriction consistent with a prior report [3]. In prior epidemiologic studies [1, 2], a higher incidence of stones among subjects in the lowest quintile of calcium intake was attributed to reduced binding of oxalate in the bowel during calcium restriction that increased urinary oxalate excretion. The lack of a change in urinary oxalate disclosed here suggests that a simultaneous dietary oxalate restriction may overcome the so-called "calcium-oxalate interaction" in the bowel and avert compensatory rise in urinary oxalate during calcium restriction.

One might have expected that the reduced urinary calcium in a setting of unaltered urinary oxalate would have produced an equivalent decline in urinary saturation of calcium oxalate. Such was not the case, since RSR of calcium oxalate decreased less prominently compared to the

fall in urinary calcium, or not at all, following dietary modification. We offer the following metabolic and physicochemical alterations for this finding.

As described under the section on calculation of activity products in **Methods**, urinary saturation of calcium oxalate is estimated from the activity product of calcium oxalate ($\alpha_{Ca^{2+}} \times \alpha_{Ox^{2-}}$), where the ionic activity ($\alpha_{Ca^{2+}}$ or $\alpha_{Ox^{2-}}$) is the product of concentration of calcium or oxalate ion and activity coefficient γ. Dietary modification can modify the activity product, by altering the formation of soluble complexes that affect the concentration of calcium and oxalate ions, and by changing γ.

During dietary modification, urinary citrate decreased, probably due to reduced dietary alkali load from avoidance of dairy products. This conclusion is supported by reduced urinary pH, and tendency toward higher urinary ammonium. Thus, the amount of calcium-citrate complexes decreased. The amount of calcium-oxalate complex also decreased during dietary modification from the decline in urinary calcium without a change in urinary oxalate. The reduced complex formation meant that less of total calcium or oxalate was complexed, leaving a relatively higher amount of $[Ca^{2+}]$ or $[Ox^{2-}]$. Urinary sodium substantially declined during dietary modification, reflective of sodium restriction. Since sodium is the main cation of urine, urinary ionic strength decreased with reduced urinary sodium, increasing γ. The increased γ led to a higher fraction of $[Ca^{2+}]$ or $[Ox^{2-}]$ as ionic activity. Thus, the decline in $\alpha_{Ca^{2+}}$ following dietary modification was less marked compared with the fall in urinary calcium, owing to reduced complexation and an increase in γ. Conversely, α_{Ox2^-} slightly increased with dietary modification because of unaltered total oxalate, reduced calcium oxalate complex, and an increase in γ.

Due to above physicochemical changes, $\alpha_{Ca^{2+}} \times \alpha_{Ox^{2-}}$ decreased less prominently than the decline in urinary calcium during dietary modification. In group I with moderate-severe hypercalciuria, the decline in RSR of calcium oxalate of 12% was still significant, though less than the fall in urinary calcium of 29%. RSR declined slightly by 6% in group II with mild hypercalciuria, compared with 19% in urinary calcium. In group III with normocalciuria, RSR did not change significantly, whereas urinary calcium declined by 10%.

The effects of dietary modification on the RSR brushite and monosodium urate were more consistent among the 3 groups. Besides reducing urinary calcium, dietary modification decreased urinary phosphorus and lowered urinary pH (which reduced dissociation of phosphate). Thus, RSR of brushite decreased significantly with dietary modification. The decline was still greater in hypercalciuric groups (31% and 22%) than in normocalciuria (17%), reflective of relative changes in urinary calcium.

Urinary uric acid decreased marginally or did not change during dietary modification. Owing largely to a decline in urinary sodium, urinary saturation of monosodium urate declined in all 3 groups. The amount of undissociated uric acid did not change following dietary modification in all 3 groups, since the decline in urinary uric acid was compensated for by reduced urinary pH (that retarded dissociation of uric acid).

The findings from this study should not be confused with an earlier analysis from our stone registry reported in this journal [5], in which urinary calcium was shown to be equally effective as urinary oxalate in enhancing the urinary saturation of calcium oxalate. That study examined the effect of calcium and oxalate alone, with patients divided according to varying ranges of urinary calcium or oxalate. In contrast, this study evaluated the effect of dietary modification in which dietary calcium as well as other components was restricted. The current effort therefore was not directed at examining the relative importance of urinary calcium and oxalate; rather, it was concerned with the examination of the effect of dietary modification that involved restriction of not only calcium but other components.

The varying hypocalciuric response to dietary modification among the 3 groups enumerated above was probably due to both metabolic and nutritional factors. The metabolic disturbance of absorptive hypercalciuria type I [24] with intestinal hyperabsorption of calcium was disclosed in 74% of patients in group I, 63% in group II, and no one in group III. The dependence of urinary calcium on dietary calcium is known to be accentuated in this condition [10]. Thus, the decrement in urinary calcium from reduced calcium intake is likely to be more prominent in hypercalciuric groups than in the normocalciuric group.

Dietary factors probably also contributed to the differences in the hypocalciuric response among the 3 groups. During the random diet, estimated calcium intake was high in 52% of patients in group I, 25% in group II, and 11% in group III. In group I, 88% of patients took more calcium during the random diet than during the restricted diet, compared with 86% in group II and 68% in group III. Moreover, the highest amounts of oxalate, sodium, and meat were ingested by patients with moderate-severe hypercalciuria (group I), intermediate amounts by those with mild hypercalciuria (group II), and lowest amounts by patients with normocalciuria (group III).

Commensurate with differing dietary intakes, group I with moderate-severe hypercalciuria displayed highest values for urinary calcium, oxalate, citrate, magnesium, phosphorus, sodium, and uric acid (during the random diet), as well as endogenous creatinine clearance, urinary creatinine, and BMI. Group II with mild hypercalciuria showed intermediate values and group III with normocalciuria lowest values. Thus, by virtually being bigger, hypercalciuric patients appeared to have consumed more food with higher amounts of calcium, oxalate, alkali, magnesium, phosphorus, sodium, and purines.

Probably reflective of varying intakes during the random diet, the decrement in urinary sodium and phosphorus following dietary modification was more prominent in hypercalciuric groups than in the normocalciuric group. It is well known that sodium restriction (as shown by reduced urinary sodium) lowers urinary calcium [11], especially among patients with hypercalciuria. Thus, the more prominent decline in urinary sodium could have contributed to the greater decrement in urinary calcium in groups I and II compared with group III. On the other hand, a reduced phosphate intake (shown by a decline in urinary phosphorus) is believed to increase urinary calcium [25, 26]. The more prominent reduction in urinary phosphorus among hypercalciuric groups may have opposed the effect of sodium cited above.

Thus, the more prominent hypocalciuric response to dietary modification in hypercalciuric groups compared to the normocalciuric group probably reflects enhanced intestinal calcium absorption, a higher intake of calcium and other nutrients during the random diet, and greater decrement in certain urinary constituents (for example, sodium). In contrast, the modest decline in urinary calcium among the normocalciuric group may have resulted from the normal state of intestinal calcium absorption, a lower intake of calcium and other nutrients, and smaller decrement in certain urinary constituents.

The aforementioned analysis of dietary modification allows us to offer the following dietary-pharmacologic guidelines in the medical management of calcium nephrolithiasis. We suggest that the intake of oxalate, sodium, and meat products should be limited in all patients. We concur that a high fluid intake should be encouraged, though not applied in our dietary modification owing to its diagnostic intent. Among patients with urinary calcium >6.88 mmol/day, the dietary calcium might be restricted to about 10 mmol/day. Trichlormethiazide or indapamide might be given to further lower urinary calcium, and potassium citrate provided to avert hypokalemia and accentuate the hypocalciuric action [27]. Among patients with urinary calcium 5.00 to 6.88 mmol/day, dietary calcium might be held to about 20 mmol/day, and potassium citrate offered. Among normocalciuric patients, we suggest a liberal calcium intake, along with potassium citrate. The use of potassium citrate among patients with mild hypercalciuria and normocalciuria is justified because urinary citrate was low normal and lower in these groups than in moderate-severe hypercalciuria. Urinary calcium loss might be averted by the provision of potassium alkali [27], and urinary $[Ca^{2+}]$ might be reduced from induced hypercitraturia that augments calcium-citrate complexation. This approach is consistent with the management format imposed in 2 long-term drug trials from our group. Among patients with AH-I (analogous to group I), dietary calcium intake was held at 10 mmol/day along with restriction of oxalate and sodium, while treatment with thiazide/indapamide and potassium citrate was provided [28]. Among patients with less severe AH-I and normocalciuria, the mean dietary calcium intake was 20 mmol/day and potassium citrate treatment alone was provided [29]. Both management programs not only averted stone formation, but also maintained or increased bone density [28, 29], allaying concern over bone loss that may ensue from calcium restriction.

CONCLUSION

Secondary hyperoxaluria from calcium restriction can be avoided by concurrent oxalate restriction. The hypocalciuric response to dietary modification was greatest for patients with moderate-severe hypercalciuria, intermediate for those with mild hypercalciuria, and least for normocalciuric patients. Because of various physicochemical changes that altered $\alpha_{Ca^{2+}} \times \alpha_{Ox^{2-}}$, RSR of calcium oxalate decreased modestly in moderate-severe hypercalciuria, slightly in mild hypercalciuria, and not at all in normocalciuria. The decline in urinary saturation of brushite in the 3 groups was also less prominent in normocalciuria than in hypercalciuria, corresponding to the relative changes in urinary calcium. Assuming urinary saturations of calcium oxalate and brushite play a key role in calcium stone formation, dietary calcium restriction as a part of a broad dietary modification might have a modest value in moderate-severe hypercalciuria, slight value in mild hypercalciuria, and a negligible value in normocalciuria.

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